70. (new) A cell comprising a disruption in a target DNA sequence encoding a TRP, wherein the disruption is produc d by the method comprising:

(a) obtaining a first sequence homologous to a first region of the target DNA sequence;

(b) obtaining a second sequence homologous to a second region of the target DNA sequence

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(c)(i) providing a vector having a gene encoding a positive selection marker and further comprising one or more recombinase target sites flanking the gene encoding the positive selection marker; and

(ii) using ligation-independent cloning to insert the first and second sequences into the vector to form the construct;

wherein the positive selection marker is located between the first and second sequences in the construct;

(d) inserting the first and second sequences into a targeting construct; and

(e) introducing the targeting construct into the cell to produce a homologous recombinant such that the target DNA sequence is disrupted.

71. (new) A cell comprising a disruption in a target DNA sequence encoding a TRP, wherein the disruption is produced by the method comprising:

(a) obtaining a first sequence homologous to a first region of the target DNA sequence;

(b) obtaining a second sequence homologous to a second region of the target DNA sequence;

(c) inserting the first and second sequences into a targeting construct; and

(d) introducing the targeting construct into the cell to produce a homologous recombinant such that the target DNA sequence is disrupted;

said first sequence being SEQ ID NO:50 and said second sequence being SEQ ID NO:51.

72. (new) A cell comprising a disruption in a target DNA sequence encoding a TRP, wherein the disruption is produced by the method comprising:

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(a) obtaining a first sequence homologous to a first region of the target DNA sequence;

(b) obtaining a second sequence homologous to a second region of the target DNA sequence;

(c) inserting the first and second sequences into a targeting construct; and

(d) introducing the targeting construct into the cell to produce a homologous recombinant such that the target DNA sequence is disrupted;

said first and second sequences being obtained by a method comprising:

(i) obtaining two primers capable of hybridizing with said target, wherein the primers form the endpoints of amplification products;

(ii) providing a mouse genomic DNA library containing the target sequence;

(iii) annealing said primers to complementary sequences in said library;

(iv) amplifying said first and second sequences; and

(v) isolating the products of the amplification reaction.

73. (new) The cell of claim 72 wherein the first primer is SEQ ID NO:45.

74. (new) The cell of claim 72 wherein the second primer is SEQ ID NO:46.

75. (new) A cell comprising a homozygous disruption in a target DNA sequence encoding a TRP.

76. (new) An isolated human cell comprising a homozygous disruption in a target DNA sequence encoding a TRP.

77. (new) An isolated stem cell comprising a homozygous disruption in a target DNA sequence encoding a TRP.

A3 Cont.

78. (new) The stem cell of claim 77, wherein said stem cell is an embryonic stem cell.

79. (new) An isolated non-human blastocyst containing the embryonic stem cell of claim 78.

80. (new) A mouse comprising a heterozygous disruption in a TRP encoded by T243 or a naturally occurring allelic variation thereof .

81. (new) A knockout mouse comprising a homozygous disruption in a target DNA sequence encoding a TRP, wherein said disruption inhibits the production of the wild type TRP.

82. (new) The knockout mouse of claim 81 wherein said TRP comprises CTG trinucleotide repeats.

83. (new) The knockout mouse of claim 82 wherein said CTG repeats encode leucine residues.

84. (new) The knockout mouse of claim 81 , wherein the disruption alters a TRP gene promoter, enhancer, or splice site such that the mouse does not express a functional TRP.

85. (new) The knockout mouse of claim 80 or claim 81 wherein the phenotype of the mouse comprises reduced weight relative to a wild type mouse which does not contain said heterozygous or said homozygous disruption.

86. (new) The knockout mouse of claim 85 wherein said reduced weight is at least about 15%.

87. (new) The knockout mouse of claim 80 or claim 81 wherein the phenotype of said mouse comprises decreased length relative to a wild type mouse which does not contain said heterozygous or said homozygous disruption.

88. (new) The knockout mouse of claim 87 wherein said decreased length is at least about 10%.

89. (new) The knockout mouse of claim 81 wherein the phenotype of said mouse comprises a decreased ratio of weight to length relative to a wild type mouse which does not contain said heterozygous or said homozygous disruption.

90. (new) The knockout mouse of claim 89 wherein said decreased ratio is at least about 20%.

91. (new) The knockout mouse of claim 81 wherein the phenotype of said mouse comprises

(a) reduced weight;

(b) decreased length; and

(c) decreased ratio of weight to length,

relative to a wild type mouse which does not contain said heterozygous or said homozygous disruption.

92. (new) The knockout mouse of claim 81, wherein the phenotype of the mouse comprises symptoms associated with cartilage disease.

93. (new) The knockout mouse of claim 81, wherein the phenotype of the mouse comprises symptoms associated with bone disease.

94. (new) The knockout mouse of claim 81, wherein the phenotype of the mouse comprises symptoms associated with kidney disease.

95. (new) A method of identifying agents capable of affecting a phenotype of a knockout mouse comprising:

(a) administering a putative agent to the knockout mouse of claim 81;

(b) measuring the response of the mouse to the putative agent;

(c) comparing the response with that of a wild type mouse; and

(d) identifying the agent capable of affecting a phenotype of a knockout mouse.

96. (new) An agent identified according to the method of claim 95.

97. (new) A method of determining whether expansion of the trinucleotide repeat in a gene encoding a TRP produces a phenotypic change comprising:

(a) providing the cell of claim 70 and a synthetic nucleic acid comprising trinucleotide repeats flanked by recombinase target sites;

(b) contacting said cell with said synthetic nucleic acid in the presence of a recombinase which recognizes said recombinase target sites, such that recombination occurs between the synthetic nucleic acid, thereby producing a transgenic cell;

(c) comparing the phenotype of said transgenic cell with a wild type cell; and

(d) determining whether trinucleotide expansion produces a phenotypic change.

All n
Serial No. **09/696,686**

98. (new) The method of claim 97, wherein said trinucl otide repeats comprise CTG.

99. (new) The method of claim 97, wherein said method comprises the use of a Cre recombinase-lox target system.

100. (new) The method of claim 97, wherein said method comprises the use of a FLP recombinase-FRT target system.

101. (new) A method of identifying agents capable of affecting a phenotype of a knockout cell line comprising:

A3 Cont

(a) contacting the knockout cell comprising a disruption in a target DNA sequence encoding a TRP with a putative agent;

(b) measuring the response of the cell to the putative agent; and

(c) comparing the response with that of a wild type cell;

(d) thereby identifying the agent capable of affecting a phenotype of a knockout cell.

102. (new) A cell line comprising a nucleic acid sequence encoding a TRP operably linked to a promoter functional in said cell line.

103. (new) The cell line of claim 102, wherein the TRP is encoded by T243 or a naturally occurring allelic variation thereof .

104. (new) The cell line according to claim 103, wherein the TRP consists essentially of the amino acid sequence SEQ ID NO:52 or a naturally occurring allelic variation thereof.